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sulfonyl halide groups, thiol groups, amine groups, sulfhydryl groups, alkene groups, and epoxide groups.

Summary of the Interview

Applicants wish to thank Examiner Helms for extending the courtesy of the telephonic interview held on March 17, 2003, with Applicants' representatives Carol A. Fang and Jeffry S. Mann. During the interview, a number of issues were clarified which have helped Applicants to more fully address the concerns of the Examiner. In particular, amendments to clarify and define the scope of the claims were discussed.

Status of the Claims

After entry of this amendment, claims 1-3, 10-11, 14-25, and 30-44 are pending in the above-referenced patent application. Claims 10 and 11 are deemed to be in condition for allowance. Applicants acknowledge and appreciate the Examiner's statement that claims 10 and 11 are allowable. Claim 14 has been amended to recite "mutant of the antibody deposited as ATCC Deposit No. PTA-4696." Support for this amendment is found in the specification at, e.g., page 73, line 5 to page 74, line 12. Claims 1 and 42-43 have been amended to recite "six complementarity determining regions," "wherein the reactive site is the mutation," and specific functional groups.

Support for these amendments is found in the specification at, e.g., page 13, line 33 to page 13, line 11; page 23, line 20 to page 31, line 14, and page 63, line 24 to page 64, line 24. Claim 25 has been amended to recite "six complementarity determining regions," and "wherein the cysteine is the mutation." Support for these amendments is found in the specification at, e.g., page 13, line 33 to page 13, line 11; page 23, line 20 to page 31, line 14; and page 63, line 24 to page 64, line 24. New claim 44 has been added. Support for new claim 44 is found at, e.g., claim 14 as filed. Thus, no new matter has been introduced by these amendments.

For the convenience of the Examiner, a marked-up version of the changes made to the claims by the present Amendment is attached as Appendix A. In addition, all of the pending claims are attached as Appendix B.

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In the present Office Action, the pending claims were rejected, in various combinations, under 35 U.S.C. § 112, first paragraph, under 35 U.S.C. § 102(b) and under 35 U.S.C. § 103(a). Each of these rejections is addressed in turn below in the order set forth by the Examiner.

**Objection to the Specification**

The Examiner has objected to the specification because page 1, lines 19-20 allegedly contains embedded hyperlinks. Applicants have amended the specification to delete the embedded hyperlinks. Accordingly, Applicants respectfully request withdrawal of this objection.

**Rejections under 35 U.S.C. § 112, First Paragraph**

**Claims 1-3, 14-25, and 30-38**

Claims 1-3, 14-25, and 30-38 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled. In making the rejection, the Examiner states that the specification is enabling for a mutant antibody that comprises a reactive site not present in the wild type parent antibody wherein the mutant antibody comprises six CDRs and specifically binds to a metal chelate wherein the reactive site is in a position proximate to or within a CDR, but alleges that the specification does not reasonably provide enablement for a mutant antibody that does not comprise a full set of six CDRs. Solely to expedite prosecution, the claims have been amended to recite a mutant antibody that comprises six CDRs.

**Claim 14**

Claim 14 also stands rejected under 35 U.S.C. § 112, first paragraph, as being allegedly non-enabled. The Examiner states that the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public or (2) reproducible from the written description. In making the rejection, the Examiner states that a deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. Claim 14 recites "wherein said mutant antibody is a mutant of the antibody deposited as ATCC Deposit No. PTA-4696." As

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explained in the supplemental amendment and supporting documentation submitted on October 21, 2002 verifying the deposit of a cell comprising a nucleic acid encoding such an antibody, the deposited material is identical to the biological material described in the specification.

In view of the foregoing amendments and remarks, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 102(b)

Claims 1-3, 14, 16-19, 24, and 42 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Stickney *et al.*, *Immunology* 79:1979-1983 (1982). Applicants respectfully traverse this rejection.

For a rejection of claims under § 102(b) to be properly founded, the Examiner must establish that a single prior art reference discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). In *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991), the Federal Circuit held that "anticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . . *There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention.*" *Id.* at 1010 (emphasis added). Anticipation can be found, therefore, only when a cited reference discloses *all* of the elements, features or limitations of the presently claimed invention.

As explained above, and during the interview, the present invention is directed to a mutant antibody comprising: (1) a reactive site not present on the wild type antibody, and (2) a CDR that specifically binds to a metal chelate. The reactive site is the mutation and interacts with a reactive group selected from carboxyl groups, hydroxyl groups, haloalkyl groups, dienophile groups, aldehyde groups, ketone groups, sulfonyl halide groups, thiol groups, amine groups, sulfhydryl groups, alkene groups, and epoxide groups.

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In making this rejection, the Examiner has alleged that Stickney *et al.* teaches a reactive SH group not present in the wild type antibody.

As discussed during the interview of March 17, 2003, Stickney *et al.* describes a (Fab')<sub>2</sub> bifunctional antibody coupled by a stable thioether linkage (*see, e.g.*, page 6650, col. 2, lines 7-9, Figure 1, legend, and abstract, line 10-12). In contrast to the present invention, Stickney does not describe or mention *any* mutant antibodies. In further contrast to the presently claimed mutant antibody, the antibody of Stickney *et al.* does not have a reactive site that is a mutation or a reactive site that interacts with a reactive group selected from carboxyl groups, hydroxyl groups, haloalkyl groups, dienophile groups, aldehyde groups, ketone groups, sulfonyl halide groups, thiol groups, amine groups, sulfhydryl groups, alkene groups, and epoxide groups. Thus, Stickney *et al.* does not disclose a mutant antibody comprising a reactive site that is not present in the wild type of the antibody, wherein reactive site is the mutation as disclosed and claimed in the present invention. Thus, an element of the presently claimed invention is absent from the disclosure of Stickney *et al.*

In view of the foregoing, Applicants respectfully submit that since Stickney *et al.*, does not disclose *all* of the elements, features or limitations of the presently claimed invention, Stickney *et al.*, cannot form the proper basis for a § 102(b) rejection and respectfully request withdrawal of this rejection.

Rejections under 35 U.S.C. § 103(a)

Claims 1-3, 14, 16-20, 22-23, 25, 30-34, 37, and 38 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Reardan *et al.*, *Nature* 316:265-267 (1985) and further in view of Orlandi *et al.*, *Proc. Nat'l. Acad. Sci. USA* 86:3833-3837 (1989), Pastan *et al.* (U.S. Patent No. 5,747,654), and Goodwin *et al.*, *J. Nucl. Med.* 29:226-234 (1988). Applicants respectfully traverse this rejection.

As set forth in M.P.E.P. § 2143, "[t]o establish a *prima facie* case of obviousness, *three* basic criteria must be met. *First*, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to

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one of ordinary skill in the art, to modify the reference or to combine reference teachings. *Second*, there must be a reasonable expectation of success. *Finally*, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

All three elements set forth above must be present in order to establish a *prima facie* case of obviousness. As explained herein below, Applicants assert that a *prima facie* case of obviousness has not been established because the cited references do not teach or suggest all the claim limitations. Moreover, one of skill in the art would have no motivation to combine the cited references. Finally, even if the disclosures of the cited references were combined, the combination would not lead to the presently claimed invention.

As explained above, and during the interview of March 17, 2003, the present invention is directed to a mutant antibody comprising: (1) a reactive site not present on the wild type antibody, and (2) CDRs that specifically bind to a metal chelate. The reactive site is in a position proximate to or within the complementarity determining regions. The reactive site is the mutation and interacts with a reactive group selected from carboxyl groups, hydroxyl groups, haloalkyl groups, dienophile groups, aldehyde groups, ketone groups, sulfonyl halide groups, thiol groups, amine groups, sulfhydryl groups, alkene groups, and epoxide groups.

In making this rejection, the Examiner alleges that Reardan *et al.* teaches antibodies to metal chelates, but acknowledges that Reardan *et al.* does not teach a mutant antibody comprising a reactive site that is not in the wild-type antibody.

The Examiner alleges that Orlandi *et al.*, Pastan *et al.*, and Goodwin *et al.* remedy the deficiency in Reardan *et al.* Specifically, the Examiner alleges that Orlandi *et al.* teach a method of cloning the variable domains of an antibody; Pastan *et al.* teach a disulfide stabilized antibody; and that Goodwin *et al.* teach a chelate comprising a reactive functional group of complementary reactivity to the reactive site. The Examiner

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concludes that it would have been obvious to use a metal chelate antibody of Reardan *et al.* and Goodwin *et al.* and protein sequence of the V<sub>H</sub> and V<sub>L</sub> as taught by Orlandi *et al.* to produce a mutant antibody comprising a reactive site not present in the wild type of the antibody.

*The Combination of References Fails to Disclose Each Element of the Applicant's Claimed Invention*

As explained above, the present invention is directed to a mutant antibody comprising: (1) a reactive site not present on the wild type antibody, and (2) CDRs that recognizes a metal chelate. The reactive site is in a position proximate to or within the complementarity determining region. The reactive site is the mutation and interacts with a reactive group selected from carboxyl groups, hydroxyl groups, haloalkyl groups, dienophile groups, aldehyde groups, ketone groups, sulfonyl halide groups, thiol groups, amine groups, sulfhydryl groups, alkene groups, and epoxide groups. Applicants respectfully assert that the combination of the references does not disclose or suggest all of the elements of the present invention.

Reardan *et al.* discloses generation of wild type monoclonal antibodies specific for the EDTA chelate of indium. As previously acknowledged by the Examiner, Reardan *et al.* contains no suggestion of a mutant antibody comprising a reactive site that is not in the wild-type antibody.

Orlandi *et al.* discloses amplifying the wild type variable regions of antibodies. Orlandi *et al.* contains no suggestion of *any* mutant antibody and, therefore, no suggestion of a mutant antibody that comprises a reactive site not present in the wild type antibody wherein the reactive site is the mutation.

Pastan *et al.* discloses stabilized polypeptide molecules comprising a first variable region of a ligand binding moiety bound through a disulfide bond to a second separate variable region of the ligand binding moiety (*see, e.g.*, col. 1, lines 61-66 and col. 2, line 12). Pastan *et al.* contains no suggestion of a mutant antibody comprising a reactive site not present in the wild-type of said antibody, wherein the CDRs recognize a metal chelate or portions thereof, and wherein the reactive site is the mutation and

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interacts with a reactive group selected from carboxyl groups, hydroxyl groups, haloalkyl groups, dienophile groups, aldehyde groups, ketone groups, sulfonyl halide groups, thiol groups, amine groups, sulfhydryl groups, alkene groups, and epoxide groups.

Goodwin *et al.* discloses wild-type monoclonal antibodies, *i.e.*, *non*-mutant antibodies, that bind to a 1,4, dithiol spacer group (*see, e.g.*, page 228, col. 2, lines 1-2) of a metal chelate. Goodwin *et al.* contains no mention or suggestion of *any* reactive site on an antibody. In addition, Goodwin *et al.* is devoid of a mention or suggestion of *any* mutant antibody, much less a mutant antibody comprising a reactive site that is not in the wild-type antibody wherein the reactive site is the mutation. In further contrast to the presently claimed mutant antibody, the wild type antibody of Goodwin *et al.* does not bind to a metal chelate comprising a reactive functional group of complementary reactivity to the reactive site of said antibody because the antibody of Goodwin *et al.* does not comprise *any* reactive site.

Thus, an element of the claimed invention is absent from each of the cited references. Specifically, none of the cited references mentions or suggests a mutant antibody that comprises a reactive site not present on the wild type antibody wherein the reactive site is the mutation. In the absence of a disclosure or suggestion of each claimed element, a proper *prima facie* case of obviousness has not been set forth. As explained in detail below, even if the references were combined, the combination would not lead to the claimed invention.

*One Of Skill In The Art Would Have No Motivation To Combine The Cited References*

The rejection points to a statement in Pastan *et al.* that "the small polypeptide of invention affords [sic] a number of advantages of the use of larger fragments or entire antibody molecules" and to the disclosure of Goodwin *et al.* that their antibody can be used for imaging as motivation for combining the disclosures of all the cited references. However, *neither* Pastan *et al.* nor Goodwin *et al.* contains any mention or suggestion of a mutant antibody having a reactive site not present on the wild-type

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antibody wherein the mutation is the reactive site and interacts with a reactive group selected from carboxyl groups, hydroxyl groups, haloalkyl groups, dienophile groups, aldehyde groups, ketone groups, sulfonyl halide groups, thiol groups, amine groups, sulfhydryl groups, alkene groups, and epoxide groups as disclosed and claimed in the present invention. Thus, only the application of improper hindsight would lead to a skilled artisan to combine Reardan *et al.*, Orlandi *et al.*, Pastan *et al.*, and Goodwin *et al.* None of the cited references provides any catalyst that would motivate one of skill in the art to combine the references. In the absence of any mention or suggestion that the methods may be combined, the skilled artisan would not be motivated to make such a combination.

Even if the cited references were combined, the combination would not lead to the presently claimed mutant antibody comprising a reactive site not present on the wild type antibody and CDRs that recognize a metal chelate wherein the reactive site is the mutation and wherein the reactive site is selected from carboxyl groups, hydroxyl groups, haloalkyls, dienophiles, aldehydes, ketones, sulfonyl halides, amines, alkenes, and epoxides because, as discussed in detail above, elements of the presently claimed antibody are absent from *all* of the disclosures of Reardan *et al.*, Orlandi *et al.*, Pastan *et al.*, and Goodwin *et al.* Specifically, none of the cited references discloses or suggests a mutant antibody having a reactive group not present on the wild-type antibody wherein the reactive site is the mutation and interacts with a reactive group selected from carboxyl groups, hydroxyl groups, haloalkyl groups, dienophile groups, aldehyde groups, ketone groups, sulfonyl halide groups, thiol groups, amine groups, sulfhydryl groups, alkene groups, and epoxide groups as disclosed and claimed in the present invention. Thus, the combination of the cited references would not lead to the presently claimed mutant antibody comprising a reactive site not present on the wild type antibody wherein the reactive site is the mutation.



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*One Of Skill In The Art Would Have No Reasonable Expectation of Success in  
Producing the Claimed Antibody by Modifying the Cited References*

One of skill in the art would have no reasonable expectation of success in modifying the disclosures of the references to produce the claimed mutant antibody having a reactive site not present in the wild-type of the antibody and six CDRs that recognize a metal chelate, wherein the reactive site is the mutation and interacts with a reactive group selected from carboxyl groups, hydroxyl groups, haloalkyl groups, dienophile groups, aldehyde groups, ketone groups, sulfonyl halide groups, thiol groups, amine groups, sulfhydryl groups, alkene groups, and epoxide groups. The rejection cites Pastan *et al.* as teaching that multiple disulfide stabilized antibodies may be constructed and concludes that one of skill in the art would have a reasonable expectation of success in modifying the references to produce the claimed mutant antibody. Pastan *et al.*, however, contains no suggestion that a reactive group on a mutant antibody may be placed in a location that would allow the reactive site on the antibody to react with a reactive group on a metal chelate bound by the antibody. Without the explicit guidance in the specification of the present application regarding the placement of a reactive site on a mutant antibody having a reactive site not present on the wild-type antibody, wherein the reactive site is the mutation and interacts with a reactive group selected from carboxyl groups, hydroxyl groups, haloalkyl groups, dienophile groups, aldehyde groups, ketone groups, sulfonyl halide groups, thiol groups, amine groups, sulfhydryl groups, alkene groups, and epoxide groups, one of skill in the art would not have expected that modifying the cited references would successfully produce such an antibody.

NOT  
IN  
CLAIMS

*The Rejection of Claims 17 And 31 Is Based on an Erroneous Interpretation That  
the Targeting Moiety Is the Same as the Antibody*

In making this rejection, the Examiner maintains that claims 17 and 31 are interpreted to mean that the targeting moiety can be the same as the antibody and alleges that the cited art reads on claims 17 and 31. Applicants respectfully disagree. First, Applicants note that claims 17 and 31 recite that the mutant antibody further comprises a

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targeting moiety covalently attached thereto. Thus, the claim language indicates that the antibody and the targeting moiety are not the same. Applicants also note that the specification explicitly describes the preparation of mutant antibody-targeting moiety *conjugates*, i.e., an antibody and a targeting agent linked together, (see, e.g., page 47, lines 4-15 and page 50 line 11 to page 52, line 15). Thus, it is clear from the claims and the specification that the targeting moiety is distinct from the antibody and that the antibody and the targeting agent are two separate moieties that are linked together. Therefore, withdrawal of this aspect of the rejection is respectfully requested.

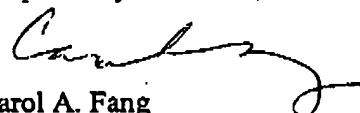
In view of the foregoing remarks, Applicants respectfully submit that the present invention is non-obvious and patentable over Reardan *et al.*, further in view of Orlandi *et al.*, Pastan *et al.*, and Goodwin *et al.* Accordingly, Applicants urge the Examiner to withdraw this rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (415)-576-0200.

Respectfully submitted,

  
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**APPENDIX A**  
**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE SPECIFICATION**

On page 1, beginning at line 17, please insert the following replacement paragraph.

Over a million new cases of cancer will be diagnosed this year in the United States [(see, for example, American Cancer Society; [http://www.cancer.org/statistics/cff98/basicfact\\_toc.html](http://www.cancer.org/statistics/cff98/basicfact_toc.html); National Cancer Institute; [http://rex.nci.nih.gov/NCI\\_Pub\\_Interface/raterisk/ratestoc.html](http://rex.nci.nih.gov/NCI_Pub_Interface/raterisk/ratestoc.html) [http://rex.nci.nih.gov/NCI\\_Pub\\_Interface/raterisk/ratestoc.html](http://rex.nci.nih.gov/NCI_Pub_Interface/raterisk/ratestoc.html))]]. While surgery can often provide definitive treatment of cancer in its early stages, the eradication of metastases is crucial to the cure of more advanced disease. Chemotherapeutic drugs are used in combinations for this purpose, with considerable success. Nonetheless, over half a million Americans will die from cancer this year. Progressions and relapses following surgery and chemotherapy/radiation are not uncommon, and in most cases the second line of treatment is of limited use. Despite the expenditure of large amounts of public and private resources over many years, better treatments for cancer are sorely needed.

On page 74, beginning at line 5, please insert the following replacement paragraph.

The three mutant Fabs, the native chimeric (ATCC Deposit No. PTA-4696, made September 19, 2002, at the ATCC, 10801 University Blvd. Manassas, VA 20110-2209), the S95C mutant and the N96C mutant, were expressed by cotransfection in S2 cells of the plasmid bearing the heavy chain with a plasmid carrying one of the three differing light chains. Culture medium of each of the respective Fab expressing cell lines was analyzed by reducing SDS-PAGE followed by Western blotting with immunostaining via the C-terminal epitope tag present on the heavy chain (FIG. 16). This staining process shows a band at 26kD as expected. ELISA analysis of the culture medium samples with indium benzyl-EDTA-HSA conjugate coated plates demonstrated that all chimeric Fabs bound the hapten in a concentration dependent manner (FIG. 17).

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IN THE CLAIMS

1                   1.       (Twice amended) A mutant antibody comprising a reactive site not present in  
2 the wild-type of said antibody and six complementarity determining regions (CDRs) [a  
3 complementarity-determining region (CDR)] that recognize [recognizes] a metal chelate or portions  
4 thereof, wherein said reactive site is in a position proximate to or within said complementarity-  
5 determining [region] regions,  
6                   wherein said reactive site is the mutation and,  
7                   wherein said reactive site interacts with a reactive group selected from carboxyl  
8 groups, hydroxyl groups, haloalkyl groups, dienophile groups, aldehyde groups, ketone groups,  
9 sulfonyl halide groups, thiol groups, amine groups, sulfhydryl groups, alkene groups, and epoxide  
10 groups.

1                   14.       (Twice amended) The mutant antibody according to claim 1, wherein said  
2 mutant antibody is a mutant of [CHA255] the antibody deposited as ATCC Deposit No. PTA-4696.

1                   22.       (Once amended) The mutant antibody according to claim 20, wherein said  
2 reactive [site] group of said chelate is an acrylamido moiety.

1                   25.       (Twice amended) A mutant antibody comprising a cysteine residue not  
2 present in the wild-type of said antibody and six complementarity determining regions (CDRs) [a  
3 complementarity-determining region (CDR)] that recognize [recognizes] a metal chelate or portions  
4 thereof, wherein said cysteine is in a position proximate to or within said complementarity-  
5 determining[region] regions, wherein said cysteine residue is the mutation.

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1                   42.     (Once amended) A mutant antibody comprising a reactive site not present in  
2 the wild-type of said antibody and six complementarity determining regions (CDRs) [a  
3 complementarity-determining region (CDR)] that specifically bind [binds] a metal chelate, wherein  
4 said reactive site is in a position proximate to or within said complementarity-determining[region]  
5 regions,

6                   wherein said reactive site is the mutation and,  
7                   wherein said reactive site interacts with a reactive group selected from carboxyl  
8 groups, hydroxyl groups, haloalkyl groups, dienophile groups, aldehyde groups, ketone groups,  
9 sulfonyl halide groups, thiol groups, amine groups, sulfhydryl groups, alkene groups, and epoxide  
10 groups.

1                   43.     (Once amended) A mutant antibody comprising a reactive site not present in  
2 the wild-type of said antibody and six complementarity determining regions (CDRs) [a  
3 complementarity-determining region (CDR)] that recognize [recognizes] a metal chelate comprising  
4 a reactive group or portions thereof, wherein said reactive site is in a position proximate to or within  
5 said complementarity-determining region[region] regions, [and]

6                   wherein said reactive group has complementary reactivity to said reactive site of said  
7 antibody,

8                   wherein said reactive site is the mutation, and  
9                   wherein said reactive group is selected from carboxyl groups, hydroxyl groups,  
10 haloalkyl groups, dienophile groups, aldehyde groups, ketone groups, sulfonyl halide groups, thiol  
11 groups, amine groups, sulfhydryl groups, alkene groups, and epoxide groups.

1                   44.     (New) The mutant antibody according to claim 1, wherein said mutant  
2 antibody is a mutant of CHA255.